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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,347	07/21/2006	Nobuo Ichihashi	SHG-050P2-319 / OSP-20263	9707

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EXAMINER	
HOBBS, LISA JOE	
ART UNIT	PAPER NUMBER
1657	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,347	ICHIHASHI ET AL.	
	Examiner	Art Unit	
	Lisa J. Hobbs	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12,20-22,24-26,29-32 and 34-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,9-12,20-22,24-26,29-32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 July 2009 has been entered.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Receipt is also acknowledged of the certified translation of the priority document, submitted 20 July 2009.

Claim Status

Claims 9-12, 20-22, 24-26, 29-32, 34-36 are active in the case. Claims 1-8, 13-19, 23, 27-28, 33 have been cancelled by preliminary amendment. Claims 9-12, 20-22, 24-26, 29-32, 34-36 are under examination; no claims are withdrawn as drawn to a non-elected invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-12, 20-22, 24-26, 29-32, 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al., Burling (US 5,149,647 A), Kussendrager et al. (US 5,596,082 A and 6,010,698 A) and Souppe (FR 2841747, as evidenced by US 7,247,331 B2), and Lihme et al. (US 5,780,593). Uchida et al. teach "[l]actoperoxidase, secretory component and lactoferrin are separated in high purity from milk and related materials such as whey with a single cation exchange resin. After adsorption on the cation exchange resin, elution is carried out with an aqueous solution having an ionic strength and pH selected to elute each separately. Lactoperoxidase is eluted first, secretory component second and lactoferrin last. Each is obtained in a purity of about 80% or greater. The cation exchange resin can be a cross-linked

polysaccharide, cellulose or an acrylamide resin having carboxyl, sulfonic acid or phosphoric acid functional groups which may be attached with a spacer" (abstract) and "[t]he eluted lactoperoxidase, secretory component, and lactoferrin solutions were concentrated separately using an ultrafiltration membrane having molecular weight cut-off of 50,000 down to 1.5 L volume, desalted to give electroconductivity of 0.2 mS/cm with an electrodialysis membrane and lyophilized to give 19.7 g of lactoperoxidase at purity of 85%" (Example 3).

Burling teaches that "[t]he microfiltered milk serum is then passed at a high rate (about 1-1.5 bed volumes per minute) through a column packed with a strong cation exchanger which selectively adsorbs lactoperoxidase and lactoferrin. The elution of the ion exchange mass is started by washing the milk serum out of the column with a buffer, preferably a phosphate buffer at the pH of the milk serum, 6.5. Subsequently, impurities, if any, are eluted with a buffer solution containing a weak saline solution, preferably of an inorganic alkali, alkaline earth or ammonium salt, for example 0.075 M NaCl. After this preparatory elution, the desired proteins are selectively eluted with buffer solutions containing saline solutions selected from the above-mentioned salts, at different concentrations. Thus, the elution of lactoperoxidase is performed at a salt concentration in the range of 0.10-0.4 M, and of lactoferrin at a salt concentration within 0.5-2 M. After this treatment, the proteins concerned have been concentrated about 500 times. The pure protein fractions are collected, and then a further concentration is preferably effected by ultrafiltration followed by desalination and freeze-drying so as to obtain a commercial product consisting of about 90% pure protein fractions" (col. 3, line 42 - col. 4, line 17 .

Kussendrager et al. teach "lactoferrin and lactoperoxidase can be eminently recovered from milk or milk products on an industrial scale [when] adsorbed to a cation exchanger by

passing milk or a milk product at a high superficial velocity (more than 500 cm per hour) and at a high liquid load (100-600 bed volumes per hour) over the cation exchanger and then eluting the cation exchanger with a number of salt solutions of different concentrations. Thus a lactoferrin-containing fraction and a lactoperoxidase-containing fraction are obtained, which can be further treated in a conventional manner" (col. 1, lines 15-25) and that "[t]he cation exchanger to which the components from the milk or milk derivative are adsorbed can be any conventional cation exchanger in this field of the art" (col. 3, lines 23-25). They teach "elution with a solution of a low NaCl concentration, for instance of between 0.15 and 0.25 molar, yields a fraction containing substantially lactoperoxidase" (col. 4, lines 1-3). As well, Kussendrager et al. state that "[t]he fractions obtained, containing substantially lactoferrin and lactoperoxidase respectively, can be further treated according to conventional methods. These methods can comprise the steps of desalting, concentration, removing bacteria, and drying" (col. 4, lines 16-18). Also disclosed is that "the binding capacity of the ion exchanger is more than 10 g lactoperoxidase and more than 10 g lactoferrin per liter bed volume, and wherein more than 80% of the lactoperoxidase and lactoferrin is extracted" (claim 3).

Souppe teaches "a process for isolating milk proteins from milk or whey comprising the following steps: a) the milk or the whey is sterilized and defatted; b) the milk fraction derived from step a) is passed over a cation-exchange resin conditioned in an elution column; c) the fraction retained on the resin is eluted with an aqueous salt solution; d) the eluate resulting from step c) is desalted, preferably by ultrafiltration and diafiltration, and then sterilized, preferably by microfiltration" (US col. 2, lines 44-54). Souppe teaches the use of strong acid groups, but

discloses that separation of milk proteins can comprise methods "such as electrodialysis or passage over weak anionic and cationic resins" (US col. 5, lines 22-23).

Lihme et al. teach "method[s] of isolating a biomolecule such as a protein or peptide from a medium containing biomolecules by ion exchange" (abstract) wherein the biomolecule can be lactoperoxidase (claim 4). They teach that "it was observed that ion exchangers of the weak type e.g. non-quarternary amine based anion exchangers such as diethylaminoethyl (DEAE)-based ion exchangers and carboxylic acid based cation exchangers can be eluted so that the neutralization of the ion exchanging (charged) groups on the ion exchange resin provide an uncharged resin. Further, it was observed that a gradual neutralization of the charged ion exchanging groups functioning as a buffer substance ensured that the bound and released biomolecule was kept in a medium having a low salt content and non-extreme pH-values which were acceptable to the eluted biomolecules. This gradual neutralization is against the general teaching of ion exchange chromatography… where anion exchangers are taught to be eluted with a decreasing pH gradient and cation exchangers are taught to be eluted with an increasing pH gradient. Further, this ensures that no buffer substances are required in the eluant, because the buffering effect is associated with the ion exchanging groups of the ion exchanger" (col. 4, lines 12-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Uchida et al., Burling et al., Kussendrager et al., Souppe, and Lihme et al. to achieve the invention as recited in the instant claims. There is much prior art disclosing the use of weak cation exchange columns of any desired capacity to adsorb lactoperoxidase and then eluting the enzyme with salt solutions of any desired ionic strength.

Subsequent treatment of the lactoperoxidase to concentrate the protein fraction is also known in the art, including ultrafiltration, to achieve a pure, solid lactoperoxidase of 80% or more.

Response to Arguments

Applicant's arguments filed 31 December 2008 have been fully considered but they are not persuasive. Applicants argue that the addition of a protein concentration range to the independent claim overcomes the teachings of the prior art. Applicants now recite in claim 9 that a range of leaching solution of ionic strength 0.07 – 0.3 is used to obtain a final 0.9 to 15% protein content when concentrating the lactoperoxidase (LP) leaching solution, i.e., LP column eluant, using an ultrafiltration membrane, wherein the impurities in the solution are then precipitated. Applicants argue that this step and concentration range is not taught in the prior art and that a combination of the cited art: Uchida, Burling, Kessendrager, Souppe, and Lihme fails to make obvious Applicant's process for producing [LP] as now recited in claim 9. It is also argued that each reference does not teach the claimed range of leaching solution that will result in the proper concentration of protein, which is asserted as having particularly beneficial effects.

However, Uchida et al. teach that after elution of each desired species "[t]he resultant [LP], secretory component [SC], and/or lactoferrin [LF] solutions are concentrated, desalted or dried, if necessary. The concentration is carried out by various methods such as evaporation under vacuum, ultra-filtration and reverse osmotic pressure filtration. The desalination is performed by conventional methods and techniques such as ultrafiltration, dialysis tube, electrodialysis, ion-exchanger resin and gel filtration. The drying is done by lyophilization, spray drying and so forth" combined and performed as desired by the skilled artisan (col. 6, lines 11-

20). In each example, they teach that the eluted LP, SC, and LF were concentrated and desalted with an ultrafiltration membrane; it is well known in the art that the concentration of an eluant using ultrafiltration membranes may be halted at any desired point in order to achieve a desired amount of protein still remaining in the eluant buffer.

Particularly, in Example 3, Uchida et al. ultrafilter "down to 1.5L volume" and then desalt. In Example 4, they desalt and then concentrate to a desired LP amount. They state that "isolation and purification of lactoperoxidase, secretory component, and lactoferrin by the present invention, requires no repeated chromatographic isolation and purification procedures and can be performed by simple methods. That is, the present invention gave lactoperoxidase, secretory component, and lactoferrin at purity of 80% or over in a single chromatographic treatment. Additional treatment with an ultrafiltration eliminates a small amount of low molecular weight fraction [e.g., impurities] and provides lactoperoxidase, secretory component, and lactoferrin at purity of 85% or over" (col. 8, lines 5-15). Thus, using washing and ultrafiltration to remove impurities is known in the prior art, whether by filtration separation or precipitation; washing solutions and desalting column buffers are known to be very low ionic strength, as is the range currently cited for the leaching solution.

Kussendrager et al. teach recovery of the eluant comprising the LP and subsequent ultrafiltration to remove impurities away from the LP solution, which ultrafiltration may be halted at any time, as disclosed by Uchida et al. and known to those of skill in the art, thus leaving the protein at any desired concentration. Kussendrager et al. teach that "[o]ne of the further treatments to which the growth factor-enriched fraction can be subjected is desalting. After the elution with the salt solutions, the fraction containing the desired growth factors will

contain a considerable amount of salt, in particular NaCl. In a number of applications of the growth factors, the presence of these salts can be undesired. Desalting can be carried out utilizing electrodialysis or ultrafiltration" (col. 4, lines 35-42). As discussed in the rejection, they teach the same desalting steps with the LP and LF fractions; a desalting step removes impurities to the preciptant fraction, away from the protein fraction. They also teach that skilled artisans may combine steps such as elution and ultrafiltration to achieve desired concentrations, etc. "It will not be necessary or desired in all cases to carry out all five operations. In a given situation, the skilled person will be able to determine which operations are to be carried out in which order, depending on the application of the material obtained" (col. 5, lines 20-25).

It appears from some arguments presented that applicant is intending to claim that a solution of LP within this concentration range automatically results in a precipitant comprising impurities and that the LP fraction can be removed from this precipitant. This is not clear from the language of the claim; read with its broadest interpretation, the claim could be reciting that filtration separation to a certain percent protein, not completely to "dry", allows impurities to be removed into a separate fraction where they then precipitate, or it could be reciting, reading in light of p. 16 of the specification, that an ultracentrifugation membrane is chosen commensurate with the passage of LP but not the passage of undesirable proteins, which would be retained on the membrane, or it could be reciting that precipitation is initiated, "effected", in the total protein fraction, including LP and other proteins and other chemicals such as salt, at certain percentages of protein.

If this any of these is the case, then one of skill would expect that if the same sequence of process steps, (1) - (4) which are generally well-known steps, are followed that the precipitation

will be effected by any of the means discussed, and then precipitate with impurities may be removed (5) from the LP fraction. There is no defining step, buffer or chemical currently recited in steps (1) – (4) that distinguishes this process from the processes discussed above and in the other cited prior art.

Thus, if LP remains in solution at 0.9 to 15% concentration while impurities spontaneously precipitate, or if a non-viscous solution of proteins comprising LP is ultracentrifuged using a membrane of a size known to allow passage of LP but not larger impurities, which would remain as a precipitant on the filter, or impurities move through certain membranes and precipitate in the eluant while the LP remains in the retained eluant buffer, then this precipitation would occur when any skilled artisan performed the ultracentrifugation step at a volume comprising a percentage of protein within this large range, which is indicated (p. 17) as comprising levels up to those known to cause concern about increased viscosity. One of skill would know to choose ultracentrifuge conditions that result in a separable protein solution, not one with such viscosity that there is a concern. One of skill particularly knows that concentration steps can be stopped at a desired volume, as is taught by Uchida et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Hobbs whose telephone number is 571-272-3373. The examiner can normally be reached on Hotelling - Generally, 9-6 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lisa J. Hobbs/
Primary Examiner
Art Unit 1657

ljh